



# InterLINCing Chromatin Organization and Mechanobiology in Laminopathies

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## Abstract

**Purpose of review** In this review, we explore the chromatin-related consequences of laminopathy-linked mutations through the lens of mechanotransduction.

**Recent findings** Multiple studies have highlighted the role of the nuclear lamina in maintaining the integrity of the nucleus. The lamina also has a critical role in 3D genome organization. Mutations in lamina proteins associated with various laminopathies result in the loss of organization of DNA at the nuclear periphery. However, it remains unclear if or how these two aspects of lamin function are connected. Recent data suggests that unlinking the cytoskeleton from the nuclear lamina may be beneficial to slow progress of deleterious phenotypes observed in laminopathies.

**Summary** In this review, we highlight emerging data that suggest interlinked chromatin- and mechanical biology-related pathways are interconnected in the pathogenesis of laminopathies.

**Keywords** Lamin · Laminopathy · Epigenetics · Mechanobiology

## Introduction: The Nucleus Organizes Chromatin

The nucleus is a complex organelle that encloses, organizes, and regulates multiple aspects of the genome. Metazoan nuclei feature a meshwork of proteins at the inner nuclear

membrane surface termed the “nuclear lamina” [1]. The nuclear lamina provides integrity to the nucleus and acts as a scaffold for chromatin organization [1–5]. Pathogenic mutations and haploinsufficiency in genes encoding nuclear lamina proteins, particularly *LMNA*, result in a collection of syndromes referred to as laminopathies, which includes myopathies, lipodystrophies, neuropathies, and segmental progeroid syndromes [6]. Laminopathies are associated with loss of chromatin organization [7–10, 11•, 12], compromised signal transduction [13–16], and aberrant mechanical transduction (hereafter mechanotransduction) [17–19]. In this review, we examine the chromatin-related consequences of laminopathy-linked mutations through the lens of mechanotransduction, highlighting emerging data that suggest interlinked chromatin- and mechanical biology-related pathways are at the nexus of laminopathy pathogenesis.

Within the context of laminopathies, we will first discuss the normal role of the nuclear lamina in chromatin organization before exploring the impact of mechanical forces on lamina-mediated organization. The nuclear lamina is critical for normal epigenetic gene regulation and genome organization [1, 20, 21]. Chromatin is radially organized within the nucleus, with some chromatin regions positioned at the nuclear periphery versus other regions more centrally positioned within the nucleus. A subset of peripheral chromatin

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physically contacts the nuclear lamina, in regions termed lamina-associated domains (LADs) [22]. In studies using various forms of genomic mapping, LADs comprise ~30–40% of the total genome and are highly gene depleted [22–24]. Moreover, genes localized within LADs are typically transcriptionally silenced and enriched for hallmarks of heterochromatin, including di- and trimethylation of lysine 9 on histone H3 (H3K9me2 and H3K9me3) [22, 25, 26]. Therefore, it is unsurprising that pathogenic or haploinsufficient *LMNA* mutations, which are linked to laminopathies, have adverse effects on the epigenome [27]. In brief, across various models, pathogenic *LMNA* mutations or reductions have been linked to aberrant changes in higher order chromatin organization, LAD positioning, DNA methylation, distribution of post-translational histone modifications, heterochromatin localization, and transcription. We refer readers to other recent reviews for additional details [7, 23, 28]. While the specific mechanisms underlying these defects remain the subject of study, it is generally appreciated that reductions or defects in nuclear lamins are linked to a weakened nuclear membrane [29, 30], which itself is a critical factor in responding to mechanical stress and cues [19], as discussed next.

### Nuclear Organization and Mechanotransduction: Mechanical Signals are Sensed by the Nucleus and Impact Genome Organization

Cells and tissues are continually exposed to stress from various sources. Mechanical stress can result in alterations to the structure and function of cells, including rapid transcriptional responses, in a process referred to as mechanosensing [31]. Mechanically-induced stimuli are transduced by structural elements of the cellular membrane, cytoplasm, and nuclear envelope, as well as mechanosensing nuclear ligands and signal transduction factors in both the cytoplasm and nucleus, ultimately converging on transcriptional responses. Extensive studies have explored the impact of mechanical stress on cells and are well-reviewed [17, 31, 32], and we highlight key studies supporting the hypothesis that the nucleus can directly or indirectly respond to extracellular forces. First, the Ingber group established that external force impacts normal nuclear shape. The team demonstrated that micropipette indentation on the surface of endothelial cells resulted in significant nuclear deformation [33]. Other foundational work from the Discher laboratory revealed that the stiffness of the nuclear lamina matrix, via concentration changes of nuclear lamins, scales with the amount of mechanical stress in specific tissue types [34]. These data strongly indicate that nuclei can both sense and respond to differing amounts of physiological mechanical stress. Reciprocally, in an *ex vivo*

cartilage study, enzymatic degradation of factors contributing to extracellular forces resulted in a reduction of nuclear membrane stiffness [35], again suggesting a functional link between mechanical force and nuclear response.

In considering the role of the nuclear membrane in chromatin organization, several studies provide specific support for chromatin changes in response to mechanical force changes. In a custom-culture neuronal cell model, repeated high impulse mechanical loading resulted in increased dynamic nuclear response, deformations in nuclei, and chromatin displacement [36]. Similarly, mesenchymal stem cells grown in a tunable hydrogel system responded to increased extracellular matrix stiffness by increasing histone acetylation (via down-regulation of histone deacetylase) and nuclear stiffness, which led to a specific osteogenic fate commitment [37]. In another hydrogel model, porcine aortic myofibroblasts that underwent persistent activation from stiff hydrogels were unable to deactivate, even after the stimulus was removed. Moreover, following persistent activation, myofibroblasts developed condensed chromatin and reduced chromatin accessibility, attributed to decreased histone acetylation by upregulation of histone deacetylase [38]. These and other studies strongly indicate a role for the nuclear lamina in maintaining normal genome integrity and organization in response to extracellular mechanical stress.

### Defects in Nuclear Lamins may Impact Mechanosensing

It is paramount to understand how normal levels of mechanical force or stress are impacted in laminopathies, where defects in normal nuclear lamina components weaken the nucleus, affect genome integrity, and are consequently associated with chromatin organization changes. It is noteworthy that cells with pathogenic laminopathy mutations or reductions in normal lamina components result in defective nuclear mechanosensing and exciting to address how this defect may be linked to disease pathogenesis. To this end, nuclear viscoelasticity is decreased in lamin A/C knockout mouse embryonic fibroblasts (using magnetic nanorods) [39]. Similarly, our group has shown reductions in viscoelasticity in human induced pluripotent stem cell (hiPSC) derived cardiac myocytes harboring pathogenic *LMNA* mutations [11•]. Nevertheless, it remains unanswered if cytoplasm-nuclear force communication plays a role in these phenotypes and if mutations in other components of mechanosensing machinery result in similar pathogenic phenotypes.

The studies highlighted above showcase the impact of manipulating extracellular force on nuclei, but it is important to consider how *normal* mechanical load and extracellular forces are linked to the nucleus. In higher eukaryotes, force

propagated through the cytoskeleton is “communicated” to the nucleus by the linker of nucleoskeleton and cytoskeleton (LINC) complex, a protein network comprised of emerin (*EMD*), SUN (*SUN1* and *SUN2*) and nesprin (*SYNE1* and *SYNE2*) proteins [40, 41]. The LINC complex physically connects to the nuclear lamina via SUN domain proteins and to the cytoskeleton via the KASH domain of the nesprin family proteins [42]. Directly relevant to this review, several groups have demonstrated an epistatic relationship between the LINC complex and lamin A/C in various models, as outlined below.

First, in a murine model, laminopathy phenotypes and reduced lifespan observed upon global *Lmna* loss were significantly ameliorated with global deletion of *Sun1* [43]. More recently, the Stewart laboratory utilized a conditional *Lmna* knockout murine model to expand this observation. They confirmed that organism-wide *Lmna* deletion in a *Sun1*<sup>-/-</sup> background doubled the lifespan of the mouse and further showed that cardiac-specific *Lmna* deletion in a *Sun1*<sup>-/-</sup> background ameliorated gross nuclear defects and organizational changes in cardiomyocytes, significantly reducing cardiac pathology [44••]. The authors then employed a dominant-negative SUN1 protein that uncoupled SUN-nesprin interactions. Expression of the dominant-negative SUN1 protein in *Lmna* deficient mice phenocopied *Sun1* deletion, suggesting that lamin A/C deficiency requires the LINC complex-associated role of SUN1 or that prevention of the lamin A/C deficiency defects requires the concomitant loss of the LINC complex-associated role of SUN1. Of note, the longevity of the *Sun1*<sup>-/-</sup> mice is surprisingly relatively preserved and is indicative of considerable functional, cell type-specific, or combinatorial redundancy in force sensing factors. These studies highlight the interplay between force propagating factors and the nuclear lamina components collectively suggesting that normal mechanical force is detrimental to cells with compromised nuclear lamina integrity, which can be at least partially relieved by eliminating force sensing in the impaired nuclei.

In another recent study, researchers have shown cardiac myocytes integrate mechanical cues during differentiation, concordant with chromatin changes [45••]. Specifically, the team showed that intranuclear mechanical tension spatially correlates with H3K9me3-marked chromatin. Changes in nuclear deformation, either through disruption of LINC complex proteins or manipulation of normal environmental stiffness led to changes in the pattern of H3K9me3-marked chromatin by immunofluorescence. This could be due to multiple possible mechanisms, including the dissociation of H3K9me3-marked chromatin from the nuclear periphery, the redistribution of H3K9me3-marked chromatin, or the de novo formation of heterochromatin. Distinguishing these different possibilities will be critical to understand the molecular basis for how mechanobiology

impacts genome organization. The authors provided additional support for observations that chromatin organization can be abrogated by manipulating stiffness. Their work is consistent with an emerging theme that dynamic mechanical environmental cues have a functional role in cardiac differentiation [46, 47] and development, perhaps through changes to nuclear architecture.

Further underscoring this connectedness, the Goldman laboratory has demonstrated that A- and B-type lamins interact with different components of the cytoskeleton via the LINC complex to regulate various mechanical pathways in mouse embryonic fibroblasts (MEFs) [48]. Specifically, A-type lamins (lamins A and C) interact with F-actin and vimentin intermediate filaments (VIFs) to modulate cortical stiffness, cytoplasmic stiffness, and cell contractility. In contrast, the B-type lamins (lamins B1 and B2) mainly interact with VIFs to modulate cytoplasmic stiffness and cell contractility. The team then used dominant negative LINC constructs and RNA interference to specifically ablate regions of the LINC complex that interact with F-actin and VIFs, which resulted in decreased cortical stiffness or cytoplasmic stiffness, similar mechanical phenotypes to cells that lack A- or B-type lamins, respectively. These results provide additional evidence for the nuclear lamina and LINC complex working in concert to modulate the mechanical properties of a cell.

Given the compelling functional link between mechanical force and nuclear architecture, it is critical to understand what happens to a *normal* nucleus in the absence of *normal* force sensing. Intriguingly, it has been observed that patients with mutated LINC components, including mutations in the nesprin proteins SYNE1 and SYNE2, phenocopy laminopathies and can develop muscular dystrophy, dilated cardiomyopathy (DCM), and some aspects of neuropathy [49]. A mouse *Syne1* knockout model (nesprin-1 lacking the SUN protein-interacting KASH domain) showed decreased survival, attenuated growth, and aberrant nuclear positioning in skeletal muscle [50]. The authors demonstrated defects in transmission of normal force and strain in muscle fibers lacking nesprin-1, collectively suggesting that nesprin-1 is essential for normal genome organization and nuclear positioning in skeletal muscle. Similarly, targeted deletion of *Syne1* and *Syne2* in murine cardiac myocytes resulted in early onset cardiomyopathy and cells with aberrant nuclear positioning, shape, and chromatin organization [51]. In this study, deletion of either *Syne* or both ablated gene expression changes in response to mechanical stimuli, again linking normal mechanical stimulation to functional gene expression responses. The McNally laboratory generated a mouse model where the C-terminus of nesprin-1 was deleted, ablating all SUN-nesprin-1 protein interactions [52]. Homozygous mutant mice exhibited significant lethality and surviving mice had severe limb muscle and cardiac defects. Additionally, the Prosser laboratory has demonstrated that desmin, a muscle-specific intermediate

filament, is required to maintain normal gross nuclear morphology and LAD-mediated genome organization via interactions with LINC complex proteins in rat cardiac myocytes [53].

### Aberrant Chromatin Organization may Link Mechanosensing- and Lamina-Mediated Laminopathy Disease Progression

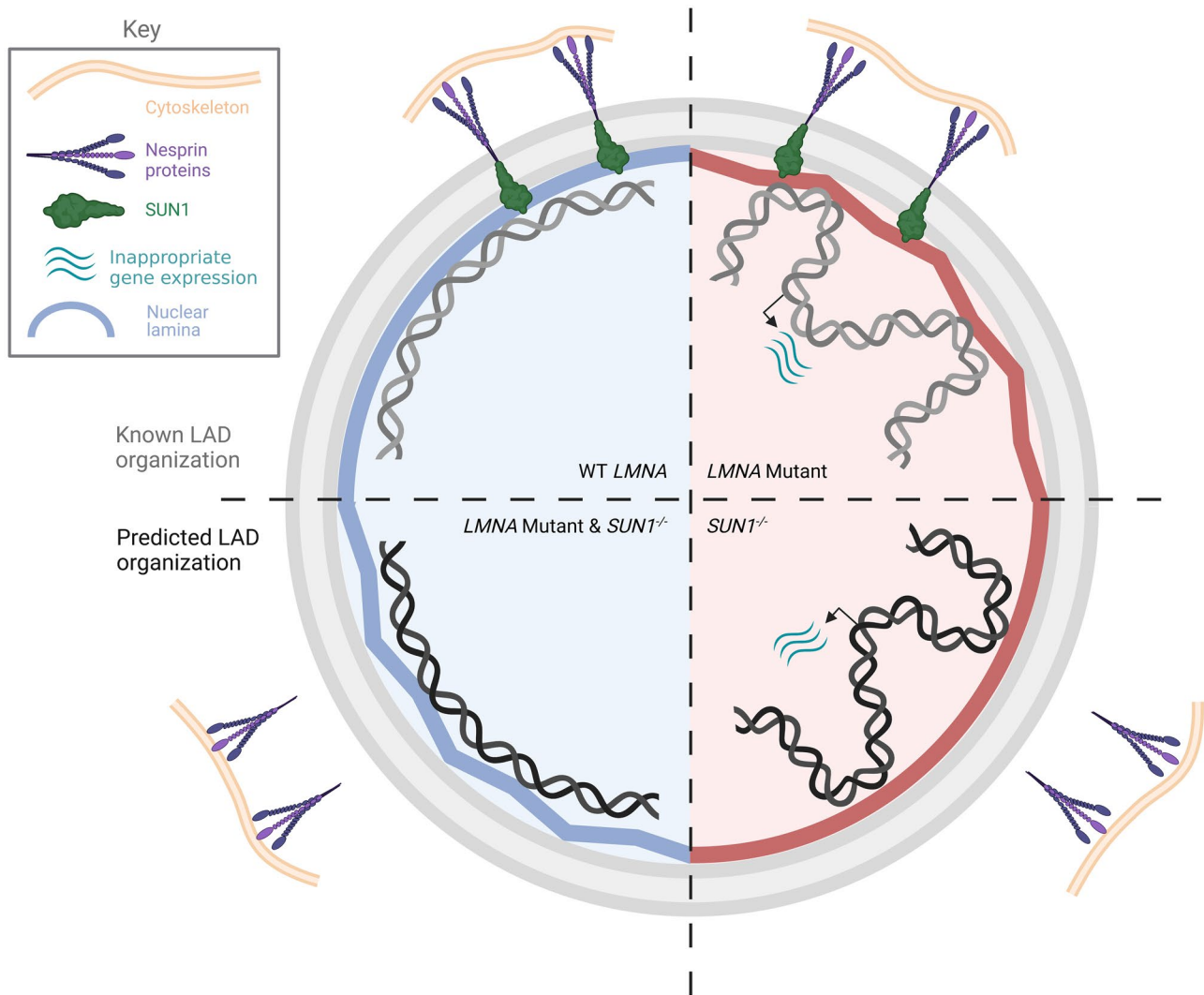
The chromatin organization defects in pathogenic *LMNA* mutants, the link between mechanosensing proteins and the nuclear lamina, the role of normal mechanical cues to functional chromatin organization changes, the overlap of phenotypes in pathogenic *LMNA* and *SYNE* mutations, and the ability to ameliorate a murine laminopathy by the deletion of a force sensing LINC protein collectively raise the interesting possibility that mechanical and lamina/chromatin-mediated mechanisms are linked in the manifestation of laminopathies. This connection is starting to be more closely examined, including work by the Wickstrom laboratory, which has determined that chromatin can alter its own mechanical state to maintain genome integrity in response to nuclear deformation [54••]. Specifically, the team showed that cells counteract mechanical stretch that deforms the nucleus by reducing H3K9me3-marked heterochromatin. They also show that persistent stretch can result in adaptation of cells within tissues to redistribute mechanical force, allowing cells to restore normal chromatin states. Relatedly, the Mauck and Lakadamyali laboratories showed that changes in the substrate stiffness of tenocytes and mesenchymal stromal cells were linked to changes in chromatin compaction, which were reversible in healthy cells by dynamically stiffening the substrate [55].

Repeated mechanical stress and nuclear rupture causes DNA damage [56]. Laminopathy models have suggested that *LMNA* mutations weaken the nuclear lamina, causing both increased nuclear rupture and DNA damage that likely contribute to disease pathology [57, 58•]. Notably, the specific laminopathy Hutchinson-Gilford Progeria Syndrome, is a disease of accelerated aging and prominently features a high degree of DNA damage [59], and the link between laminopathies and DNA damage is an exciting and well-reviewed area research [60]. Of interest to the scope of this review, both lamins A/C and LINC complex components promote DNA damage repair [61–63]. Further, the Lammerding laboratory recently showed mechanical trauma of *Lmna* mutant myocytes caused nuclear envelope rupture and DNA damage [58•]. When the research team disrupted the LINC complex via dominant negative KASH, this ameliorated rupture and improved contractility. They further showed that muscle biopsies taken from patients with *LMNA* muscular dystrophy also demonstrated an increased DNA damage phenotype. Taken together, these results emphasize a role for mechanically-induced DNA damage in laminopathy pathophysiology and

disease progress, opening the exciting possibility that such a pathway could be considered for therapeutic targeting to improve disease outcomes, should DNA damage be an important contributor to laminopathy phenotypes [64].

Collectively, these studies strongly support the idea that a function shared by the LINC complex and lamin proteins is affected by mechanical stress. One possible model is that mechanical force, as sensed by LINC complex components, is critical for normal genome organization through the connection to an intact nuclear lamina (Fig. 1). In pathogenic *LMNA* mutant cells or in cells with reduced *LMNA* levels, the normal lamina integrity is compromised, resulting in gross nuclear abnormalities, DNA damage, and loss of LADs [8, 11•]. Therefore, one can speculate that gross nuclear morphology and chromatin organization defects may be the result of normal mechanical force no longer being tolerated or properly sensed in cells with compromised nuclear lamina integrity (Fig. 1, top right). This model provides exciting opportunities to test aspects of the mechanosensing and lamina connection to better understand their interplay in laminopathy disease progression. First, as discussed above, loss of nesprin proteins results in some laminopathy-like phenotypes. This suggests that mechanosensing is also required to maintain normal genome organization and nuclear integrity, even in the presence of otherwise normal nuclear lamina components (Fig. 1, bottom right). However, this has not been empirically demonstrated and the molecular similarities and differences between mutations in nesprin versus lamin proteins also remain unknown. An initial step in understanding this connection is to map LADs in cells either lacking individual nesprin proteins, expressing the aforementioned dominant-negative peptides, or harboring patient-inspired mutations. If LADs are lost, are they similar to those LADs lost in pathogenic *LMNA* mutants? If so, it is compelling to focus future studies on understanding temporal dynamics of this dissociation and if similar gene expression changes are linked to this LAD dissociation.

Relatedly, as presented above, mechanical force that results in nuclear deformation results in release of peripheral heterochromatin to maintain nuclear integrity, shearing, or rupture [54••]. In *LMNA* mutants, it is possible that the normal amount of mechanical force upon a nucleus can no longer be tolerated because the lamina itself is fragile and mechanically strained [18] and no longer appropriately scaled with the normal amount of force [19, 34]. This can be tested by uncoupling the force sensing mechanism from the nuclear lamina. For example, in a cultured cell system, it is possible to express pathogenic *LMNA* mutants or deplete *LMNA* in cells where *SUN1* is also deleted, or to express the aforementioned dominant-negative peptides that uncouple nesprin-SUN interactions. If gross nuclear morphology and LAD organization are preserved, this would suggest that a nucleus with impaired strength or integrity manifests morphology and organization defects



**Fig. 1** Model: Mechanical force is critical for normal genome organization. Top left: Wild type cells exhibit normal force transduction to the nucleus via the LINC complex and have normal LADs at the nuclear periphery. Top right: Cells with perturbations of the nuclear lamina via mutations in *LMNA* feature compromised LADs and aberrant upregulation of non-lineage genes. Bottom right: Cells with perturbations to the LINC complex via *SUN1* deletion may demonstrate

compromised LAD organization, leading to aberrant gene expression and failure to properly respond to mechanical stimuli. Bottom left: Perturbation of the LINC complex in *LMNA* mutant conditions may preserve LAD organization and prevent abnormal gene expression, based on observations of *Lmna* mutant defects (partially) ameliorated with concomitant *SUN1* loss. Figure created with BioRender.com

because it cannot properly withstand normal levels of mechanical stress or force (Fig. 1, bottom left). Of note, this experiment would be designed to preserve normal nuclear morphology and organization upon abrogating lamina integrity. It is much more challenging to consider a situation in which abnormal LAD organization would be restored after it was disrupted. To date, it remains elusive how LADs become established each cell cycle, and proteins that tether LADs to the nuclear periphery are also mostly unknown in mammalian cells [65, 66]. Moreover, cardiac cells are post-mitotic, and it is not yet clear if it is possible for LAD organization to change without

a cell cycle. These and similar efforts underway by many research teams will continue to uncover additional critical factors, mechanisms, and pathways impacted in laminopathies, revealing the interlinked contributions of chromatin organization and mechanosensing in disease progression.

## Conclusion

The nuclear lamina plays multiple integral roles in the cell, including providing structural support for the nucleus and integrating cytoskeletal forces impinging on the LINC

complex and nuclear envelope. In the nucleus, the lamina plays an important scaffold for chromatin to be organized in three-dimensional space. Emerging data suggests an intricate interplay between these various functions that may contribute to development and disease.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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